Translation

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference BLOcp263/85P	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/FR2003/003413	International filing date (*day/month/year*) 18 novembre 2003 (18.11.2003)	Priority date (*day/month/year*) 18 novembre 2002 (18.11.2002)
International Patent Classification (IPC) or national classification and IPC C12N 15/12		
Applicant COMMISSARIAT A L'ENERGIE ATOMIQUE		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 7 sheets. including this cover sheet.

☒ This report is also accompanied by ANNEXES. i.e.. sheets of the description. claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of 7 sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☐ Non-establishment of opinion with regard to novelty. inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty. inventive step or industrial applicability: citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

Date of submission of the demand 09 juin 2004 (09.06.2004)	Date of completion of this report 15 February 2005 (15.02.2005)
Name and mailing address of the IPEA/EP Facsimile No.	Authorized officer Telephone No.

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/FR2003/003413

I. Basis of the report

1. With regard to the **elements** of the international application:*

☐ the international application as originally filed

☒ the description:

pages 1-32 . as originally filed
pages _____ . filed with the demand
pages _____ . filed with the letter of _____

☒ the claims:

pages 1-5 . as originally filed
pages _____ . as amended (together with any statement under Article 19
pages _____ . filed with the demand
pages _____ . filed with the letter of _____

☒ the drawings:

pages _____ . as originally filed
pages _____ . filed with the demand
pages 1-38 . filed with the letter of 13 January 2005 (13.01.2005)

☐ the sequence listing part of the description:

pages _____ . as originally filed
pages _____ . filed with the demand
pages _____ . filed with the letter of _____

2. With regard to the **language**. all the elements marked above were available or furnished to this Authority in the language in which the international application was filed. unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language _____ which is:

☐ the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).

☐ the language of publication of the international application (under Rule 48.3(b)).

☐ the language of the translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/ or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application. the international preliminary examination was carried out on the basis of the sequence listing:

☐ contained in the international application in written form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. ☐ The amendments have resulted in the cancellation of:

☐ the description. pages _____

☐ the claims. Nos. _____

☐ the drawings. sheets/fig _____

5. ☐ This report has been established as if (some of) the amendments had not been made. since they have been considered to go beyond the disclosure as filed. as indicated in the Supplemental Box (Rule 70.2(c)).**

* *Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rule 70.16 and 70.17).*

** *Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.*

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	1-38	YES
	Claims	None	NO
Inventive step (IS)	Claims	1-7, 28-32, 35, 37	YES
	Claims	8-27, 33, 34, 36, 38	NO
Industrial applicability (IA)	Claims	1-38	YES
	Claims	None	NO

2. Citations and explanations

Reference is made to the following documents:

D1: TOMITA T: 'New markers for pancreatic islets and islet cell tumors' PATHOLOGY INTERNATIONAL 2002 JAPAN, vol. 52, no. 7, 2002, pages 435-432, XP002246605 ISSN: 1320-5463

D2: WO 02/24733 A (BURGESS CATHERINE E; MALYANKAR URIEL M (US); SYPTEK KIMBERLY ANN, 28 March 2002 (2002-03-28)

1. Novelty (PCT Article 33(1) and (2))

1.1 No mention of the use of a polynucleotide having the sequence SEQ ID No. 1 as marker for the beta cells of the islets of Langerhans was found in the prior art. Therefore the subject matter of claims 1 to 7 and 28 to 32 is novel (PCT Article 33(2)).

1.2 The subject matter of claim 8(b) includes all the polynucleotides comprising a fragment of at least 20 consecutive nucleotides having SEQ ID. No.1, apart from those in which this fragment is itself already

included in the sequences having access numbers (NCBI) AX526723, AX526725 and AX526727 (and which comprise at least 15 consecutive bases of said sequences). SEQ ID No. 1 differs from sequences AX526723, AX526725 and AX526727 in at least positions 52 and 367 of SEQ ID No. 1. It follows that the scope of claim 8(b) is limited to fragments having at least 20 consecutive nucleotides of SEQ ID No. 1 and of which the sequence comprises at least the base in position 52 or that in position 367 of SEQ ID No. 1. Although several polynucleotides (e.g. genomic clones) having these characteristics can be found in the prior art, the International Preliminary Examining Authority recognizes that the term "can be used according to claim 1" implies certain features (e.g. concerning their size) that exclude these polynucleotides from the scope of claim 8. Therefore the subject matter of claims 8 to 27 and 33 to 38 also meets the requirements of PCT Article 33(1) and (2).

2. Inventive step (PCT Article (1) and (3))

2.1 **D1**, which is considered to represent the prior art closest to the subject matter of claim 1, describes (pages 426 to 428) the use of the glucose carrier GLUT-2 as marker for the beta cells of the islets of Langerhans. The subject matter of claim 1 differs from this method by the structure (sequence) of said marker. The problem addressed by the present invention can thus be considered that of providing an additional marker for the beta cells of the islets of Langerhans.

The solution proposed in claim 1 of the present application is considered to involve an inventive step (PCT Article 33(3)) since the prior art does not contain any obvious method of isolating a new marker of this type or any indication that the zinc carrier encoded by sequence SEQ ID No. 1 is expressed selectively in the beta cells of the islets of Langerhans. Consequently the subject matter of claims 1 to 7, 28 to 32, 35 and 37 meets the requirements of PCT Article 33(3).

2.2 As concerns claim 8, **D2**, which is considered the closest prior art, describes (pages 6 and 7, 19 to 26, and 67 to 127) a polynucleotide encoding a zinc carrier polypeptide (NOV2) that has a sequence which is 99.2 % identical to that of the present application. This polynucleotide is expressed in several organs, including the pancreas (page 25). D2 also describes (pages 67 to 127) the probes and primers that can be used to amplify the sequence encoding NOV2.

The polynucleotides in claim 8 of the present application differ from those of D2 by their sequence, but appear nevertheless to be entirely capable of being used in a method as per claim 1 (in the same way as the possible uses of the polynucleotides in claim 8 are not restricted to those according to claim 1).

The problem addressed by the present invention can thus be defined as that of providing additional polynucleotides enabling the expression of a zinc carrier to be detected, or the sequence or part of the sequence encoding the zinc carrier to be

amplified.

The solution proposed in claim 8 of the present application is not considered inventive (PCT Article 33(3), for the following reasons:

The differences between the polynucleotides in D1 and those in claim 8 are not responsible for a particular technical effect. Therefore these polynucleotides can be considered equivalent. Obtaining an allelic variant or an equivalent of the polynucleotide in D2 is a problem which a person skilled in the art would easily solve by sequencing the NOV2-encoding gene in other individuals, as suggested in D2, in order to identify polymorphisms in this gene, which are potentially useful for research or diagnostic purposes. Therefore the subject matter of claim 8 does not involve an inventive step.

D2 also discloses a method of measuring the expression of the corresponding gene using Northern blot or RT-PCR, methods of detecting allelic variants of said sequence, a DNA chip comprising specific probes or primers for the NOV2-encoding gene, detection of the NOV2 polypeptide or of antibodies against the latter by ELISA, a vector comprising the NOV2-encoding polynucleotide, its insertion in a host cell or a transgenic animal, the use of the latter for producing the NOV2 protein and methods of screening agonist or antagonist compounds for NOV2 activity or for its expression, or of compounds capable of binding to the polynucleotide which encode it. D2 also mentions the role played by zinc carriers in monitoring cell proliferation and

survival. Hence the same reasoning as was applied to claim 8 applies to the subject matter of claims 9 to 21, 22(a) and (b), 23 to 27, 33, 34, 36 and 38, which no longer meets the requirements of PCT Article 33(3).

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

1. Claim 1 is unclear since its subject matter is defined in relation to a percentage of "similarity". As page 10 of the description indicates, the meaning of the word "similarity" depends on what is considered to be a conservative substitution. The application does not provide any tables indicating unambiguously which substitutions may or may not be conservative and provides a definition only in terms of a result to be obtained, which is, moreover, vague ("which generally does not alter the functional properties of the protein").

2. Claim 3 and dependent claims 10 and 11 contain an inconsistency since the primers having sequences SEQ ID Nos 3 and 4 both appear to belong to sequence 1 (whilst sequence SEQ ID No. 5 is part of sequence SEQ ID No. 1 and sequence SEQ ID No. 6 is complementary to SEQ ID No. 1). The primer pair according to SEQ ID Nos 3 and 4 thus does not appear to provide a solution to the technical problem addressed by the present application.

3. Claim 8(c) contains a circular reference ("defined in (c)").

4. Claim 12, which is dependent on claim 11, is unclear since it relates to a small interfering RNA "capable of being obtained by amplification" and given the usual meaning of the term "amplification" (since the product of amplification is normally a DNA, not an RNA).